REMARKS

Upon entry of this response claims 1-5, 7, 11-21, 24-25, 28-37, 40-41 and 43-45 are pending, and of these claims 1, 3, 28, and 43 are independent.

Applicants have also amended claims 1, 3, 28, and 43 to add clarity that the known genomic structure is associated with the alternative splice variants, such as exon structure or location data, protein family classification data, splice variants data, and genomic sequence data (support may be found in paragraph [0119]). Other amendments have been made for clarifying purposes as described below.

Applicants respectfully assert that no new matter is presented by these amendments. Applicants respectfully request entry of the same.

Reply to Claim Rejections – 35 U.S.C. §112, First Paragraph-Written Description

The Examiner has rejected claims 1-5, 7, 11-21, 24-25, 28-37, and 43-45 are rejected under 35 U.S.C. §112 first paragraph, regarding the written description requirement. On page 4 of the Office Action, the Examiner states that the originally filed application does not disclose iteratively fitting intensity data by itself, but is disclosed as being combined with probe data or gene structure data. Without agreeing to the propriety of the rejection, Applicants have amended the claims to require fitting probe data and intensity data to genomic structure date to obviate this rejection. Applicants believe that this amendment has overcome the present rejection and request that the Examiner reconsider and withdraw it.

Reply to Claim Rejections – 35 U.S.C. §112, First Paragraph-Enablement

Claims 1-5, 7, 11-21, 24-25, 28-37, and 43-45 are rejected under 35 U.S.C. §112 first paragraph, regarding the enablement requirement. Upon entry of the present amendments to the specification, Applicants respectfully assert that the invention is sufficiently described to enable one of ordinary skill in the related art to make and use the invention. In particular, Applicants have amended the claims to include "known genomic structure associated with the alternative splice variants, such as exon structure or location data, protein family classification data, splice variants data, and genomic sequence data".

The present claims are limited to taking the probe identifier data and intensity data and fitting them to the genomic structure data. Typically, the probe identifier and intensity data show what probes have hybridized to the target and that provides gene structure data on what exons are present for example. The data is analyzed and the output provides information such as concentration data for exons.

The Examiner asserts that it is not known how to fit "probe set identifiers and intensity values to a model of genomic structure without knowledge of fitting parameters and or criteria. The specification further does not provide guidance for how to fit (e.g. statistically, physically, etc.), what to fit (i.e. it is not know what prove set identifiers and intensity values represent), and what model to fit (genomic structure model is not known). The specification also does not provide any disclosure that the recited 'fitting' will determine ASVs." (see page 4 of the Office Action).

Applicants respectfully disagree. The incorporated text from 60/398,958 shows how to fit the data under the heading "Model Fitting and Minimization". That section uses criteria that are set by the user and can be optimized by such techniques as the

Maximum Likelihood method. Disclosure of preferred algorithms is presented. See also the discussion below regarding the Examiner's comments from page 5 regarding what model to fit.

The application also shows what to fit, as probe set identifiers and intensity values are known criteria, among others. For example, paragraph 12 of the present invention states:

> A genomic web portal is described in accordance with yet another embodiment. The portal includes an input manager that receives from a user over the Internet a selection of probe set identifiers that identify probe sets capable of detecting biological molecules. The input manager also receives hybridization intensity values corresponding to the probe set identifiers. The hybridization intensity values are produced from biological probe array experiments.

Consequently, it is evident to one of skill in the art that a probe set identifier labels a probe or set of probes for reference purposes. The above two items are recited in the specification and the claims, but there may be other items to fit that are known to those of skill in the art as well. This knowledge is gleaned, not only from the above passage, but from the common knowledge of one skilled in the art.

The intensity value is also known as follows on paragraph 10:

> The method may also include the act of receiving hybridization intensity values corresponding to the probe set identifiers. The hybridization intensity values are produced from biological probe array experiments. In such implementations, the act of determining may be based, at least in part, on the probe set identifiers and their corresponding hybridization intensity values.

Intensity values are known to one of skill in the art to be a representation of the hybridization between probe and target. In a preferred embodiment, it is a fluorescent label on the target that provides the intensity value when the target/probe combination is

viewed by a scanner. The intensity value can be a function of the concentration of target bound. (See also paragraph 120 and Fig. 11 from 60/398,958, for example). Therefore, one of skill in the art would understand what a probe set identifier and an intensity value represent.

The Examiner states on page 5 of the Office Action that the specification does not show what model to fit, i.e." a genomic structure model is not known". Applicants respectfully disagree with the Examiner and assert that one of skill in the art would understand what genomic structure would include. However, Applicants have limited the claims to types of genomic structure and therefore respectfully suggest that this rejection has been obviated and should be withdrawn.

Additionally, the Examiner states that "the specification also does not provide any disclosure that the recited 'fitting' will determine ASVs because the model fitting disclosed in application 60/398,958 only yields the relative concentration of known variants and the relative affinity of probes (page 13)". Applicants respectfully disagree.

Figure 11 of 60/398,958 shows that the model fitting of the probe intensities as correlated to the probes is an indication of the ASV. The text describing that figure states:

> Figure 11 shows the CD44 modeling results in detail. Gene structure information and probes are listed on left. The graphs on top display the actual concentration and the predicted relative concentration from modeling. The blocks in the center plot the residuals for each experiment, high residual is indicated by a blue color and low residual by red. The initial value assigned to probe affinity is shown on the left, and the relative probe affinity term derived from model fitting is shown on the right.

The passage at pages 18 and 19 of 60/398,958 describing fig 11 state:

> This example demonstrates a general model that could be used to analyze alternative splicing. Spiked CD44 transcripts in yeast background was

performed, and modeling results using the CD44 exon and junction probes are presented in Fig. 9. A near diagonal line (45 degrees) indicates good data prediction. The quality of the data fitting can also be examined by the residual. Fig. 10 shows the changes of the sum of squared differences of observed intensities and predicated intensities for all the probes in all experiments, the fast convergence to a stable state indicate a good data fitting. Fig. 11 shows the CD44modeling results in detail. Gene structure information and probes are listed on left. The graphs on top display the actual concentration and the predicted relative concentration from modeling. In, Fig. 11, the blocks in the center plot the residuals for each experiment, high residual is indicated by a blue color and low residual by red. After modeling, the residuals are noticeably lower.

In addition to relative splice variant concentration, relative probe affinity terms outputted can also be useful in improving data fitting. An illustration of this process is shown in Fig. 11. An initial arbitrary affinity term assigned to the probes yields a relative affinity term through the model. Probes with low affinity terms can then be discarded and the data refitted iteratively. In Fig. 11, the probe targeting exon 3 feature 1 should be discarded.

The analysis of the above criteria would provide to a user the information showing how fitting would determine an ASV. The general outline of the preferred embodiment in Fig. 11 shows that an iterative process is used to compare probe intensity to the genomic structure to identify ASVs. (See also the discussion in the section below regarding 'fitting'). Consequently, Applicants assert that the present application has provided sufficient enabling disclosure for the claims as currently amended. Applicants respectfully request that the Examiner reconsider and withdraw the rejections.

Reply to Claim Rejections – 35 U.S.C. §112, Second Paragraph

Claims 1-5, 7, 11-21, 24-25, 28-37, and 43-45 are rejected under 35 U.S.C. §112 second paragraph.

With respect to the rejection of claims 1 and 43, Applicants have amended the claims to recite that the intensity values relate to individual probes. With respect to the

Examiner's second point, probe set identifiers, the identifiers relate to the probe sets and not the hybridization data. See paragraph 12:

> A genomic web portal is described in accordance with yet another embodiment. The portal includes an input manager that receives from a user over the Internet a selection of probe set identifiers that identify probe sets capable of detecting biological molecules. The input manager also receives hybridization intensity values corresponding to the probe set identifiers. The hybridization intensity values are produced from biological probe array experiments.

Consequently, Applicants respectfully request that the rejections be withdrawn.

With respect to the rejection of claims 1, 3, 28, and 43, Applicants respectfully assert that the term "fitting" is described in the application with respect to fitting data to models of genomic structure (see paragraphs [0119] and [0120]). Fitting is a term often used in the optimization process. Optimization typically consists of three ingredients: an objective function, unknown variables (parameters), and constraints. The process of finding values of variables (parameters) that minimize or maximize the objective function for the data while satisfying the constraints is the optimization process. The choice of the function and the processing of apply the data to the function is often called a fitting process. Structural or statistical model/function may be included in the fitting process. Examples of a function include the least square or Maximum Likelihood methods, examples of variables are probe affinity or variant concentration, and an example of a constraint is concentration. See the incorporated text from 60/398,958.

In one preferred embodiment, the process is iterative and the output displays the comparison as described above in the discussion concerning enablement. Additionally, the present amendment to the claims further specify that the models of genomic structure are exon structure or location data, protein family classification data, splice variants data,

and genomic sequence data and that comparison. Given the above description and the current amendments, Applicants respectfully assert that one of ordinary skill in the related art would understand the limitations of fitting intensity data to a model of genomic structure in light of the description and amendments to the specification, and respectfully request that the rejections be withdrawn.

With respect to "model of genomic structure", Applicants have amended the claims to include the language to show that the genomic structure includes exon structure or location data, protein family classification data, splice variants data, and genomic sequence data. Applicants believe that this amendment overcomes the present rejection and request that the rejection be withdrawn.

CONCLUSION

In conclusion, Applicants have amended the claims to overcome several rejections. They amended the claims to recite probe set identifiers and intensity values are compared to genomic structure, which overcomes the written description rejection. Applicants have both argued and amended the claims to overcome the enablement rejection. For example, they have further specified genomic structure as including exon structure or location data, protein family classification data, splice variant data, and genomic sequence data. Applicants have also amended the claims and argued to overcome the clarity rejections to the claims. Applicants, therefore respectfully assert that each of the amended claims is currently patentable.

For these reasons, Applicants respectfully request the Examiner reconsider and withdraw the rejections. Furthermore, they believe that all pending claims are now in

condition for allowance. If the Examiner has any questions pertaining to this application or feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731 5021.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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